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Telomeric refinement of the *MCKD1* locus on chromosome 1q21[1]

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Background. Autosomal-dominant medullary cystic kidney disease type 1 (MCKD1) is a tubulointerstitial nephropathy that causes renal salt wasting and end-stage renal failure in the sixth decade of life. The chromosomal locus for MCKD1 was localized to chromosome 1q21 in a Cyprotic kindred. In this report we describe further refinement of the critical genetic region by a recombination in a Belgian kindred.

Methods. Clinical data and blood samples of 33 individuals from a large Belgian kindred were collected and high-resolution haplotype analysis was performed.

Results. In the Belgian kindred linkage to the *MCKD1* locus on chromosme 1q21 was found with a logarithm of odds (LOD) score significant for linkage. A recombination in individual III:7 for marker *D1S2624* refines the critical genetic region to 2.1 Mb. In this kindred a wide variety of clincial symptoms and age of onset of renal failure was detected.

Conclusion. We confirm the *MCKD1* locus on chromosome 1q21 and show further refinement of the *MCKD1* locus to 2.1 Mb. This allowed us to exclude another 17 genes as positional candidate genes.

Autosomal-dominant medullary cystic kidney disease (MCKD) is a progressive tubulointerstitial nephropathy. Clinical characteristics for MCKD are salt wasting, decreased urinary concentration ability, and end-stage renal disease (ESRD) [1]. In some kindreds an association with hyperuricemia was found. In MCKD small corticomedullary cysts are common, but not always detected. Kidney size is normal or slightly reduced [2]. Two gene loci for MCKD have been described. For *MCKD1* (OMIM 17400) a locus was published on chromosome 1q21 in a large Cypriotic kindred [3]. In an Italian kindred the *MCKD2* locus was localized to chromosome 16p12 [4]. Clinical symptoms are very similar in MCKD1 and 2. However, in MCKD2 gout is more frequent and there is more severe hyperuricemia. Age of onset of renal failure is 32 years of age in MCKD2 compared to 62 years in MCKD1 [4]. Otherwise, these two disease variants are clinically undistinguishable.

MCKD shows a renal histologic triad of (*1*) tubular basement disintegration, (*2*) tubular atrophy with cyst development at the corticomedullary border, and (*3*) interstitial cell infiltration associated with fibrosis [5]. Neither imaging results, nor pathologic findings are pathognomonic for MCKD. The condition shares clinical and morphologic similarities with recessive juvenile nephronophthisis (NPH) [6]. However, in NPH end-stage renal failure occurs in the first two decades of life. Moreover, NPH is inherited in an autosomal-recessive pattern, whereas MCKD is autosomal-dominant.

The *MCKD1* locus on chromosome 1q21 has been confirmed by several groups [7–10]. However, the critical genetic region could never be narrowed down sufficiently to warrant mutational analysis of positional candidate genes. For MCKD2 the responsible gene has recently been identified. Missense mutations in exons 4 and 5 of the uromodulin *(UMOD)* gene have been described in at least 20 different kindreds [11–14]. These mutations alter the encoded Tamm-Horsfall protein (THP), the most abundant protein in human urine [13]. No related candidate gene can be found in the critical chromosomal region for MCKD1 on chromosome 1q21.

METHODS

Patient recruitment

Blood samples were available from 33 individuals of a large Belgian kindred, in which MCKD segregated

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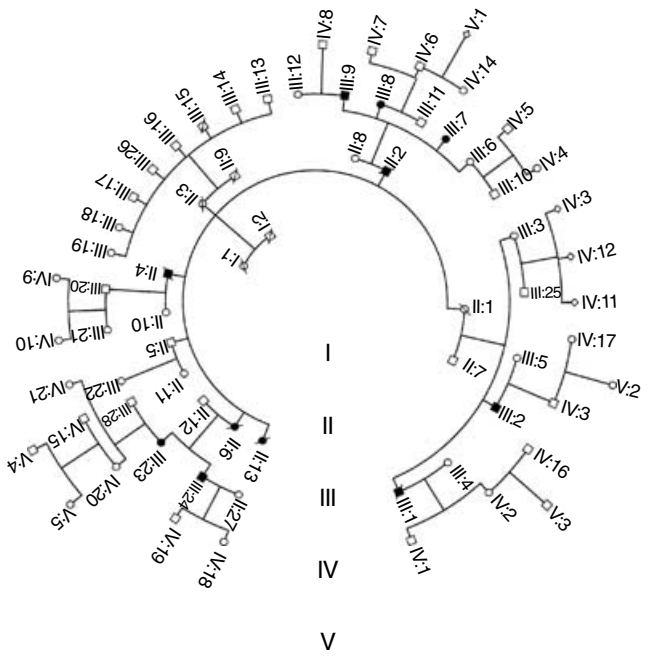

Fig. 1. Pedigree of the Belgian MCKD1 kindred. Circles denote females, squares denote males. Filled symbols denote 11 individuals affected by MCKD1, crosshatches denote deceased individuals, and question marks indicate that these indivduals are too young to exclude the diagnosis of MCKD. Roman numerals denote generations.

(Fig. 1). Clinical data were obtained from an additional four affected individuals who were deceased. The age at diagnosis, the age at onset of ESRD, hyperuricemia, imaging data, and biopsy results were reviewed, if available. Clinical criteria used for the diagnosis of MCKD were (*1*) chronic renal failure, (*2*) defective urine concentration ability (<800 mOsm/L after overnight water deprivation), polyuria (>3 L/day), (*3*) compatibility of the pedigree with autosomal-dominant inheritance, and (*4*) at least one pedigree member with chronic renal failure in whom renal biopsy showed tubular-interstitial fibrosis with infiltrates, tubular atrophy, and thickening of the tubular basement membrane. Hyperuricemia was defined as serum uric acid concentration >1 SD greater than the normal values for age and gender (both genders 5 to 10 years 4.1 ± 1 mg/dL; female 12 years 4.5 ± 0.9 mg/dL; 15 years 4.5 ± 0.9 mg/dL; and ≥18 years 4.0 ± 0.7 mg/dL; male 12 years 4.4 ± 1.1 mg/dL; 15 years 5.5 ± 1.1 mg/dL; and ≥18 years 6.2 ± 0.8) [15].

The study was approved by the ethics committees of the Albert-Ludwigs-University Freiburg and the University of Michigan. All participating family members provided informed consent.

Haplotype analysis

Genomic DNA was isolated by standard methods directly from blood samples using the QIAamp blood kit (Qiagen, Valencia, CA, USA). Haplotype analysis was performed in 33 individuals (including six affected individuals) (Fig. 1). Haplotypes were inferred from segregation in 13 additional individuals (four additional affected individuals). For haplotype analysis we used ten consecutive polymorphic microsatellite markers that span the critical *MCKD1* region in the following order: *cen – D1S305 – D1S29H23g* – D1S29H23e* – D1S29H23c* – D1S303 – D1S1595 – D1S243J18c* – D1S336K24h* – D1S336K24a* – D1S2624 – tel*. To characterize the recombination in individual III:7, eight additional markers were genotyped (*D1S1153 – D1S336mw19* – D1S336mw22* – D1S336mw25* – D1S2624mw4* – D1S2715 – D1S394 – D1S1653*) (Fig. 2). Marked with an asterisks are ten novel polymorphic makers, created by searching for microsatellite markers using a list of di-, tri-, and tetranucleotide repeats in a BLAST search (data available from the authors) [16]. To analyze linkage to the *MCKD2* locus, we performed haplotype analysis with 12 polymorphic microsatellite markers: *cen – D16S3060 – D16S764 – D16S499 – D16S3056 – D16S3036 – D16S3041 – D16S412 – D16S417 – D16S420 – D16S3113 – D16S401 – D16S3116 – tel*. Fluorescently labeled polymerase chain reaction (PCR) products were detected by a Genetic Analyzer 3100^{TM} (Applied Biosystems, Foster City, CA, USA) and were analyzed by the Genotyper^{TM} software. Two-point logarithm of odds (LOD) score calculations were performed by the Linkage program software package [17], using an autosomal-dominant model with full penetrance, and a gene frequency for MCKD1 of 0.0001. For calculations an "affecteds-only" strategy was chosen, because of the age related penetrance in MCKD1.

RESULTS

Clinical data

In this Belgian kindred 33 individuals were available for genetic analysis. In six individuals the diagnosis of MCKD was made. The clinical and laboratory findings of the patients are shown in Table 1. The age at presentation ranged from 29 to 53 years (median 41 years). Age at ESRD varied between 34 and 49 years (median 41 years). The progression from first symptoms at presentation (polyuria, polydipsia, or anemia) to ESRD varied between 6 months and 11 years (data not shown). Three individuals (III:1, III:8, and III:9) received kidney transplants at the age of 41, 43, and 50 years, respectively. Hypertension was found in one individual (III:24). Hyperuricemia was present in two individuals (III:2 and III:8). Gout was not reported in any patient. Ultrasound in four patients revealed small kidneys in two affected individuals (III:1 and III:2), and small medullary cysts in two other patients. Histology was available in indivdual III:2, exhibiting microcysts, atrophic tubuli, thickened basement

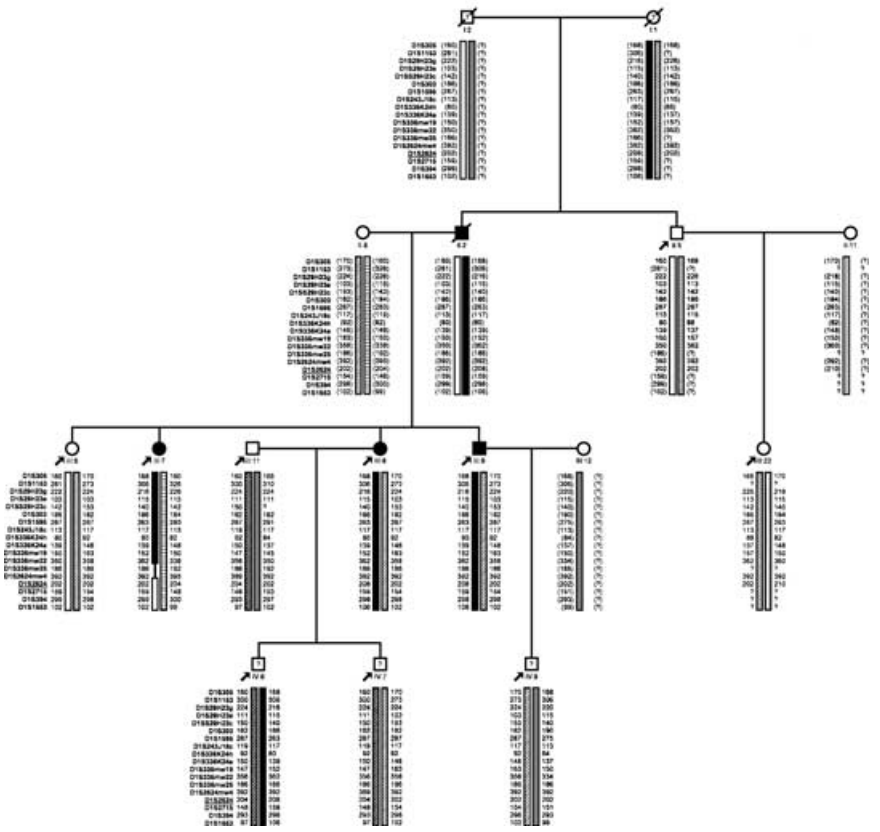

Fig. 2. Results of the haplotype analysis of 18 markers at the *MCKD1* locus in 16 individuals from the Belgian MCKD1 kindred. Circles denote females, squares denote males. Filled symbols denote affected individuals. Arrows denote individuals in whom DNA was available for haplotype analysis. Inferred haplotypes are shown in parenthesis. Differently shaded bars symbolize haplotypes. Paternal haplotypes are drawn to the left, maternal haplotypes to the right. Marker positions are indicated with left individuals. Assignment of the disease associated haplotype to I:2 is arbitrary. The black haplotype showed complete cosegregation with the phenotype in all six living affected individuals of this kindred (data not shown). The question marks in individuals IV:6 – IV:8 indicate that these persons are too young to exclude the diagnosis of MCKD. Note the recombination event in individual III:7, which identifies marker *D1S2624* as a new telomeric flanking marker. The thin line in the left haplotype of individual III:7 shows the uninformative region, which makes it impossible to distinguish between the black and the white haplotype.

Table 1. Synopsis of clinical data, imaging results, and renal histology in the Belgian MCKD1 kindred investigated

Individual	Gender	Age at presentation *years*	Age at ESRD/death *years*	Age at NTX *years*	Clinical symptoms	Creatinine clearance *mL/min/1.73 m²*	Imaging	Histology (kidney biopsy)
II:2	M	ND	34	—	CRI	ND	ND	ND
II:4	M	ND	38	—	CRI	ND	ND	ND
II:6	F	ND	ND	—	CRI	ND	ND	ND
II:13	F	ND	ND	—	CRI	ND	ND	ND
III:1	M	29	41/51	41	CRI	ND	US: small kidneys bilaterally	ND
III:2	M	38	41	—	CRI, Hyperuricemia	17.5	US/CT: small kidneys bilaterally	Global glomerulosclerosis, microcysts, atrophic tubuli, thickened basement membrane
III:7	F	53	—	—	CRI	65	US: small cysts in both kidneys, microcalcifications	ND
III:8	F	49	49	50	CRI, Hyperuricemia	ND	ND	ND
III:9	M	41	43	43	CRI	ND	ND	ND
III:23	F	40	—	—	CRI	23.5	US: multiple small medullary and cortical cysts bilaterally	ND
III:24	M	42	—	—	Mild renal insufficiency, hypertension, hyperuricemia	51	ND	ND

Abbreviations are: CRI, chronic renal insufficiency; ESRD, end-stage renal disease, ND, no data; NTX, renal transplantation; US, ultrasound.

Table 2. Two-point logarithm of odds (LOD) scores at the *MCKD1* locus for the Belgian MCKD kindred

			Two-point	LOD	score at	Θ		
Marker	0.000	0.001	0.010	0.050	0.100	0.200	0.300	0.400
D1S305	1.146	1.143	1.115	0.991	0.836	0.532	0.260	0.068
D1S29H23g	2.034	2.030	1.989	1.805	1.569	1.076	0.578	0.163
D1S29H23e	1.458	1.456	1.438	1.345	1.204	0.861	0.470	0.128
D1S29H23c	1.832	1.828	1.790	1.619	1.399	0.939	0.481	0.122
D1S303	0.469	0.467	0.451	0.380	0.299	0.162	0.066	0.014
D1S1595	1.614	1.611	1.579	1.433	1.244	0.850	0.455	0.129
D1S243J18c	1.331	1.327	1.295	1.151	0.970	0.613	0.294	0.073
D1S336K24h	1.166	1.162	1.133	1.004	0.843	0.533	0.259	0.067
D1S336K24a	0.640	0.683	0.619	0.535	0.435	0.255	0.114	0.028
D1S2624	−1.602	−0.921	−0.046	0.483	0.576	0.452	0.225	0.050

membrane, and global glomerulosclerosis, thus confirming the diagnosis of MCKD.

Linkage analysis

We were able to exclude linkage in this kindred to the *MCKD2* locus on chromosome 16p12 (data not shown). Linkage analysis with ten polymorphic markers from the critical *MCKD1* region revealed cosegregation of a haplotype of marker alleles with the affected status for MCKD. Two-point LOD scores were positive at the *MCKD1* locus. The maximum two-point LOD score was 2.034 ($\Theta = 0$) for *D1S29H23g*, thus confirming significant linkage in this kindred to the *MCKD1* locus (Table 2). In linkage studies on candidate regions where only a few polymorphic markers are tested, the criterion of significance for linkage can be relaxed to >2.0 (from >3.0 as necessary in a total genome search with multiple tests of approximately 400 markers) [17]. A recombination event in III:7 defined marker *D1S2624* as distally flanking (Fig. 2). By filling in additional eight markers the recombination was confirmed. Since marker *D1S305* was described as the centromeric flanking marker to *MCKD1* in a Welsh kindred [9], our data restrict the critical *MCKD1* region by 1.2 Mb to a minimum interval of 2.1 Mb.

DISCUSSION

In this large Belgian kindred we demonstrate linkage to the *MCKD1* locus on chromosome 1q21 and further refine the critical genetic region. Concerning the clinical data this kindred reveals an interesting difference to the previously published cases [3, 7–10]. MCKD1 has been described as leading to ESRD in the sixth decade [3, 9, 10]. Here we found a median age of 41 years at onset of ESRD, which is clearly younger than published previously. Stavrou et al [10] found that succeeding generations were affected earlier than their anchestors. They hypothesized the mechanism of genetic anticipation to be active. The earlier age of onset in our kindred would be compatible with these findings. Furthermore, we found the presence of hypertension in only one individual, which is different to a percentage of 51.4% of the affecteds described by Stavrou et al. Also Cohn et al [7] described hypertension as a common characteristic of MCKD1. We detected hyperuricemia in two individuals. Hyperuricemia was not described in the kindreds of Auranen et al [8] and Cohn et al [7]. However, Christodoulou et al [3] stated, that the two families, in which MCKD1 was initially described, had a history of gout and hyperuricemia. Stavrou et al [10] detected an elevated uric acid level in 50% of the gene carriers before onset of the disease. The generally described mild symtoms, the intrafamiliar variability concerning the age of onset and the progression to ESRD are also found in this Belgian kindred. Although cysts are not an essential criterion for the diagnosis of MCKD [2], they may be helpful in making the diagnosis. Therefore, it is remarkable to realize how early in the course of the disease cysts can appear, for example in III:7, who developed cysts in both kidneys.

Initially, the *MCKD1* region was described to be 7.1 Mb long between marker *D1S498* and *D1S2125* [3]. We previously refined the critical genetic region to 3.3 Mb with the new centromeric flanking marker *D1S305* [9]. The new telomeric recombination event we detected here in III:7 narrows down the critical genetic region to 2.1 Mb with the flanking marker *D1S2624*. An additional refinement of up to 300 kb would have been possible, if markers *D1S336mw25* and *D1S2624mw4* were not uninformative. This refinement allowed us to exclude 17 positional candidate genes from the critical genetic region.

Recently, we published an approach toward refinement of the *MCKD1* region based on the hypothesis of haplotype sharing [18]. Although this approach provides a useful opportunity to narrow down the criticial region, there is still a certain degree of insecurity, that sharing of this haplotype may have occurred by chance. This risk is eliminated by data based on true recombinations, such as we present here. The Belgian kindred studied here did not share the haplotype we described previously [18].

Within the new defined critical genetic region a variety of interesting candidates are found on the basis of similarities to the pathomechanisms of other renal cystic diseases. Mucin 1 (*MUC1*), also called peanut-reactive

urinary mucin, is a cell surface glycoprotein that is involved in actin binding and in the structure of the cytoskeleton. *MUC1* is interacting with E-cadherin and β-catenin, proteins that also colocalize and coprecipitate with polycystin-1 (*PKD1*) [19] and inversin (*INVS*) [20], which causes a similar renal histology in NPH type 2. Moreover, *MUC1* includes a variable number tandem repeat (VNTR), which might increase the propensity for spontaneous deletions. Thrombospondin 3 (*THBS3*) is involved in cell adhesion and has an epidermal growth factor (EGF)-like domain, as does *UMOD*, the protein altered in MCKD2. Additionally, Vos et al [21] demonstrated *THBS3* expression in mouse kidney, and interaction between *THBS1* and transforming growth factor-β (*TGF*-β) was published [22]. *TGF*-β is known to be involved in renal fibrosis [22], which is part of the MCKD histology. The secretory carrier membrane protein 3 (*SCAMP3*) is part of the post-Golgi transport system. In autosomal-dominant polycystic kidney disease (ADPKD) altered Golgi function and impaired basolateral exocytosis in renal epithelia was shown [23]. Furthermore, *SCAMP3* and epidermal growth factor receptor (*EGFR*) colocalize and coimmunoprecipitate [24]. *EGFR* overexpression was described in *cpk* mice, an animal model for autosomal-recessive polycystic kidney disease (ARPKD) [25].

ASH1L encodes a putative transcripton factor that localizes to cell-cell tight junctions and to nuclei [26]. Localization to the tight junction raises a suspicion about a role in cystogenesis [27]. Interestingly, also *INVS* is localized in nuclei and is involved in the cell cycle [28]. *ARGHEF2* is a rho/rac guanine nucleotide exchange factor. Rho-related small guanosine triphosphatase (GTPases) are involved in the regulation of signal transduction cascades from extracellular stimuli to the cell nucleus and the cytoskeleton. Colocalization of the nucleotide exchange factor GEF-H1 with tubulin was shown [29]. Different kinds of tubulins form microtubuli, which are the "backbone" of cilia. Proteins that are altered in renal ocular diseases such as *PKD1*, *PKD2* [30], *NPHP1,* and *NPHP2* [31] have been detected in cilia. Moreover, coimmunoprecipitation of *NPHP1* and *INVS* with β-tubulin was shown [32]. Misato belongs to the tubulin/FtsZ family, which includes als α-, β-, and γ-tubulin. FtsZ is the prokaryotic ancestor of eukaryotic tubulin. Therefore, misato seems to be another component of microtubuli and may be involved in the structure of cilia. Moreover, FtsZ proteins are responsible for cell division and thereby misato has functional similarities to *INVS* [32]. The chaperonin containing TCP1 subunit 3 (*CCT3*), was cloned from a human kidney cDNA library [33]. Interaction between eukaryotic chaperonin *CCT* and tubulin was described by Llorca et al [34]. *CCT3* also promotes activation of the anaphase-promoting complex, a complex in which also *INVS* interacts [35].

We hope to alleviate the gene identification in MCKD1 by the refinement of the critical region described here, and to thereby restrict the possible candiate genes.

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